Thought Leadership

COVID-19 and Fungal Infections: The Importance of Vigilant Detection Strategies

RAPID DIAGNOSTIC TOOLS ARE CRITICAL TO DIAGNOSING COINFECTIONS TO DELIVER EFFECTIVE TREATMENT AS SOON AS POSSIBLE

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Researchers are uncovering the true impact of secondary fungal infections in COVID-19 patients. However, symptoms of some fungal diseases can be similar to those of COVID-19, including fever, cough, and shortness of breath, likely contributing to the underdiagnosis of fungal coinfections. In addition, clinical mycology (the study of pathogenic fungi) remains often-underrepresented in the field of infectious diseases, where diagnosis requires significant expertise and awareness. Rapid diagnostic tools are critical to identifying and diagnosing such infections and determining the correct course of treatment as quickly as possible.

Diagnosis challenges with COVID-19 and coinfections

With SARS-CoV-2 coinfection, an individual may be infected with the virus and one or more additional pathogens concomitantly. However, there are several factors that can complicate patient diagnosis and treatment in the case of coinfection.

SARS-CoV-2 infection leads to both innate and adaptive immune responses which, in some cases of severe disease, can become dysfunctional and cause significant lung and systemic pathology. This lung damage and dysregulated immune response in severe COVID-19 pneumonia puts these patients at an increased risk of secondary infection with bacteria, fungi, or other viruses.

In addition, individuals with preexisting conditions could be more susceptible to severe COVID-19 if infected. Importantly, intensive care unit (ICU) patients with severe COVID-19 are at increased risk of nosocomial, or health care-associated, infections and should be carefully monitored as rapid treatment decisions are required, particularly in the case of multidrug resistant (MDR) microorganisms.

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Secondary infection could be easily missed and go undiagnosed in the face of a SARS-CoV-2 primary infection, especially if symptoms overlap. Diligent testing of COVID-19 patients for other infectious diseases is vital.

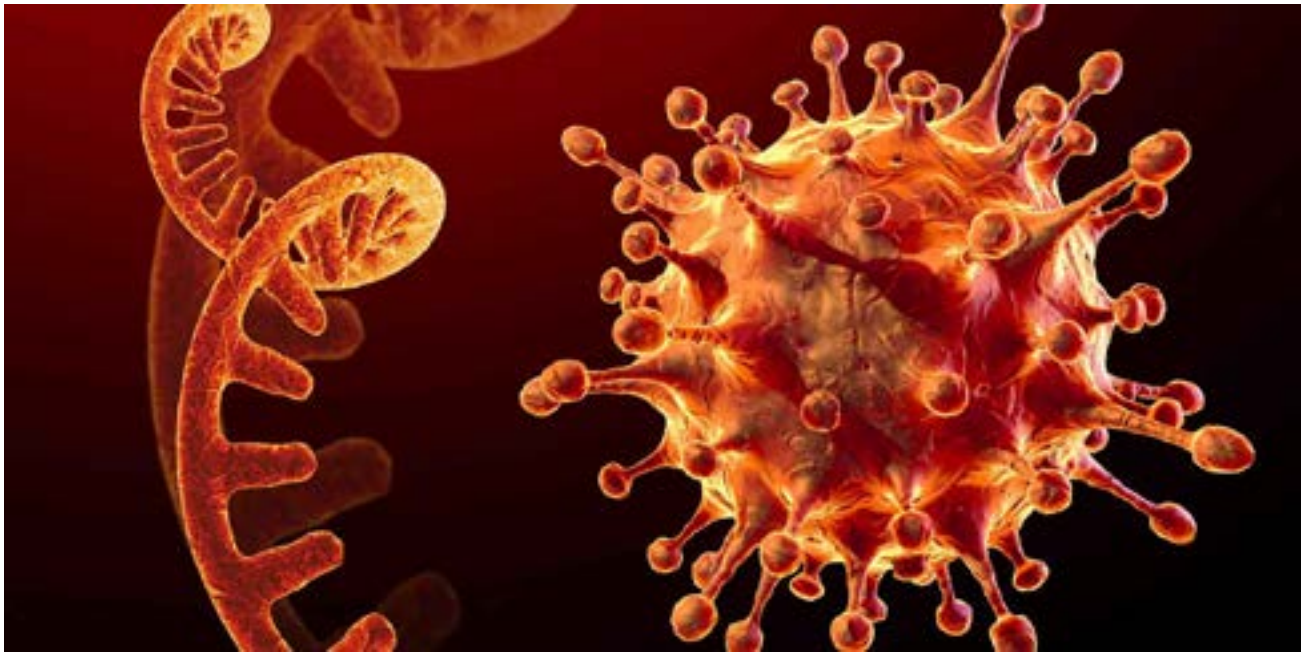
Common fungal pathogens

The main fungal pathogens identified in severe COVID-19 patients are *Aspergillus* and *Candida*, but other infrequent opportunistic species such as *Mucor* and *Cryptococcus* may also cause lung infections. Diagnosing the infecting pathogen is vital to reduce delays in antifungal treatment.

ASPERGILLOSIS

COVID-19-associated pulmonary aspergillosis (CAPA) has been the predominant fungal disease reported among COVID-19 patients with acute respiratory distress syndrome (ARDS) and many studies have assessed risk factors, incidence, and mortality rates associated with CAPA:

- **Risk factors:** Patients hospitalized in ICU for COVID-19 share risk factors and underlying diseases reported for invasive fungal infections (IFI), particularly



chronic respiratory diseases, corticosteroid therapy, intubation/mechanical ventilation, and severe immune response such as cytokine storm.

- **Incidence:** CAPA incidences vary widely—from 2 percent to 33 percent across multiple countries with differences potentially attributed to the misdiagnosis and underdiagnosis of CAPA, variable access to screening methods, and differences in treatment modalities for severe COVID-19.
- **Mortality:** Although mortality rates have varied between studies, many have reported high rates of 44 percent to 67 percent.

Invasive aspergillosis (IA) is notoriously challenging to diagnose, requiring microbiologic and/or histopathologic evidence. The European Confederation for Medical Mycology and the International Society for Human and Animal Mycology instituted a group of experts to propose consensus criteria for a case definition of CAPA and to provide up-to-date management recommendations for the diagnosis and treatment of patients with CAPA. Three different grades are proposed (i.e., possible, probable, and proven CAPA) to enable researchers to homogeneously classify patients in registries and interventional clinical trials. It is also important to consider the distinction between *Aspergillus* colonization and invasive infection, and the subsequent classification.

A review of 38 published CAPA cases highlighted the diagnostic and therapeutic challenges posed by this novel fungal coinfection and suggested that, for patients with severe COVID-19 pneumonia in critical care, a combination of two or more mycological criteria could aid in the early initiation of antifungal therapy:

- Real-time polymerase chain reaction (PCR) detection of *Aspergillus* DNA in blood or respiratory samples
- Galactomannan (GM) detection from serum, bronchoalveolar lavage fluid (BALF), or endotracheal aspirates (ETA)
- Isolation of *Aspergillus* sp. from BALF/ETA/sputa
- Serum 1-3 β-d-glucan (BDG) detection (not specific for *Aspergillus)*

This approach may aid in targeting early antifungal therapy, which has shown to reduce the mortality rate of COVID-19 patients with *Aspergillus* coinfection. Including rapid and reliable molecular testing, such as PCR, alongside other biomarkers and culture can reduce the time to diagnosis and support physicians in optimizing patient management.

Furthermore, fungal infections resistant to antifungal treatment have been described in patients with severe COVID-19, including Azole-resistant *Aspergillus* demonstrating the importance of early diagnosis and the need for resistance surveillance.

CANDIDIASIS

Patients hospitalized for COVID-19 are at risk of nosocomial infections including candidemia, or bloodstream infections caused by *Candida*. Information on invasive candidiasis complicating COVID-19 is limited, with reported incidence ranging from 0.8 percent to 14 percent and higher incidence found in ICU settings. Prolonged ICU stays, protracted invasive mechanical ventilation, extracorporeal membrane oxygenation (ECMO), broad-spectrum antimicrobial use, renal replacement therapy, and the presence and duration of central venous catheters may have played a role in the increased incidence in ICU patients.

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Candida auris is an emerging fungus that can cause outbreaks of severe infections in health care facilities. Since the start of the COVID-19 pandemic, outbreaks of *C. auris* have been reported in ICUs of acute care hospitals globally. Considering the increase of health care-associated *C. auris* outbreaks in the region of the Americas and in the context of the COVID-19 pandemic, the Pan American Health Organization/World Health Organization (PAHO/WHO) recommends that member states build capacity for early detection and effective reporting, with the goal of implementing public health measures to prevent and control its spread in health services.

Commercial methods available in standard clinical laboratories often incorrectly identify C. *auris* and, as a result, the incidence or prevalence of infections may be underestimated and its management could be inappropriate. Protein analysis, using matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (MS), with an up-to-date reference library, as well as molecular biology techniques like PCR, have shown to be the most reliable methods for correctly identifying *C. auris*.

C. auris is a MDR microorganism, and data is showing rapid development of resistance to the antifungal family echinocandins—the first line of treatment. Local resistance surveillance is imperative to guide treatment recommendations and reduce death from COVID-19 in patients with severe fungal coinfections.

Identifying and diagnosing coinfections

Rapidly identifying secondary pathogens and diagnosing fungal coinfections is vital to determine the correct course of treatment and improve patient outcomes. Molecular diagnostics microbial detection and identification tools are designed to detect the primary species associated with IA and invasive candidiasis, respectively, allowing clinical microbiologists to make fast and well-informed treatment decisions that, for critically ill COVID-19 patients, can make all the difference.

Gaining a better picture of how coinfection impacts outcomes

Research is ongoing to better understand the challenges of diagnosing and managing coinfections. However, there is not yet a clear picture of how coinfection impacts clinical outcomes or whether existing infections predispose individuals to poorer COVID-19 resilience.

As more research comes to light, microbiologists and health care professionals will gain a better understanding of coinfection and the importance of lessening the burden of these diseases in the face of the ongoing COVID-19 pandemic.